Sleep Medicine Reviews (2007) 11, 71–79

SLEEP MEDICINE reviews

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THEORETICAL REVIEW

Insomnia: Pathophysiology and implications for treatment

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KEYWORDS
Insomnia;
HPA axis;
Hyperarousal

Summary Interest in developing a greater understanding of the pathophysiogical mechanisms underlying primary insomnia has increased. Recent evidence indicates that there may be some neuroendocrine and clinical similarities between primary insomnia and major depressive disorder, that abnormal corticotropin releasing factor (CRF) activity occurs in major depression, and that CRF hyperactivity appears to mediate the hyperarousal seen in primary insomnia. These findings all point to the possibility of hypothalamic–pituitary–adrenal (HPA) axis and CRF overactivity in both disorders. More recent findings have strengthened the evidence that primary insomnia may be linked with mood disorders and is associated with HPA axis overactivity and excess secretion of CRF, adrenocorticotropin releasing hormone, and cortisol. These insights have implications for managing chronic primary insomnia, such as use of antiglucocorticoid agents.

Introduction

Despite more than 30 years of research into the nature of insomnia, our understanding of its basic pathophysiology has lagged behind that of other sleep disorders, such as narcolepsy and sleep apnea.[1] In part, this discrepancy stems from the heterogeneous nature of insomnia, which is both a primary condition with a pathophysiology, and a condition co-existing with numerous medical and psychiatric disorders. The course of the co-existing medical or psychiatric disease may be modulated by the course of the sleep disturbance.[2–4] In addition, insomnia has been found to precede the onset of major depression.[5–7]

The *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR) defines the term *primary insomnia* as difficulty initiating or maintaining sleep, or non-restorative sleep, that results in clinically significant distress or impairment in social, occupational, or other important areas of functioning (American Psychiatric Association, 2000). DSM-IV-TR specifies that primary insomnia cannot occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm disorder, or a parasomnia,

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doi:10.1016/j.smrv.2006.06.002

Table 1 DSM-IV-TR diagnostic criteria for primary insomnia.

(A) The predominant complaint is difficulty initiating or maintaining sleep, or non-restorative sleep, for at least 1 month.
(B) The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
(C) The sleep disturbance does not occur exclusively during the course of Narcolepsy, Breathing-related Sleep Disorder, Circadian Rhythm Sleep Disorder, or a Parasomnia.
(D) The disturbance does not occur exclusively during the course of another mental disorder (e.g., Major Depressive Disorder, Generalized Anxiety Disorder).
(E) The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

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or during the course of another mental disorder (e.g., major depression), and it cannot be due to a general medical condition or substance use disorder (Table 1). Primary insomnia has been conceptualized as sleep disturbance not arising from a medical, psychiatric, circadian, behavioral, or pharmacologic cause, or from a primary sleep disorder.[8]

The DSM-IV-TR criteria inform clinicians what primary insomnia is *not*, but do not define what it *is*, beyond a complaint of difficulty initiating or sustaining restful sleep lasting more than a month. It is unclear what pathophysiologic mechanisms drive primary insomnia and what implications these have for insomnia morbidity and treatment. This paper provides a brief overview of the epidemiology, morbidity, and risk factors associated with insomnia, and will also briefly highlight the specific research still needed in each of these areas. Next the paper discusses the question of primary insomnia etiology, focusing on the critical role of hyperarousal and abnormal corticosteroid regulation—a pathophysiology that may be the unifying link between primary insomnia, depression, and perhaps other disorders. Finally, the implications of this new research will be explored as it relates to insomnia pharmacotherapy.

Insomnia: epidemiology, morbidity, and risk factors

Epidemiology

Prevalence estimates for insomnia range from 10% to 50% of the adult population. Summaries of the epidemiologic evidence conclude that 10–13% of the adult population suffers from chronic insomnia, and an additional 25–35% has transient or occasional insomnia.[9,10] It is estimated that 75% of population-based chronic insomnia is associated with psychiatric and medical diseases, or with primary sleep disorders and primary insomnia accounts for approximately 25% of all chronic insomnia.[11] Thus, primary insomnia is estimated to occur in 1–2% of the general population,[11] while it accounts for as much as 25% of all chronic insomnia cases.[8]

Insomnia generally does not resolve spontaneously. Half the adult population experience trouble sleeping at some time in their life, and approximately one-third report that the problem has lasted more than a year[12]. For those with insomnia characterized by poor sleep at least 3 nights/week and subjective daytime impairment, the problem persists from 2 to 6 years;[12] durations over 2 years were typical for more than half of those reporting moderate to severe symptoms.[12] In retrospective reports, individuals with severe symptoms report having sleep difficulties for at least 1 year, with 40% suffering for more than 5 years. In various longitudinal reports, up to 80% of individuals with severe insomnia experienced no remission over time.[70]

Morbidity

Studies using standardized assessment instruments show that insomnia patients consistently report significantly decreased daytime functioning, with deficits across a large number of emotional, social, and physical domains and with a severity similar to other chronic diseases.[13–15] They describe difficulties with memory, concentration, attention, and reasoning.[16] Objective measurements, as described below, have failed to confirm these patient reports and demonstrate variable or no impairment with objective assessment.

Patients with chronic insomnia generally show signs of hyperarousal, with normal to prolonged